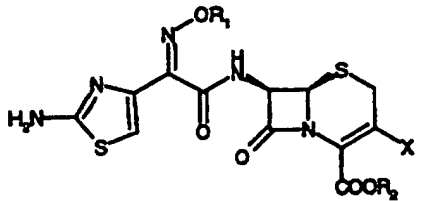


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<p>(21) International Application Number: PCT/EP00/03428</p> <p>(22) International Filing Date: 14 April 2000 (14.04.00)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">673/99</td> <td style="width: 40%;">15 April 1999 (15.04.99)</td> <td style="width: 30%;">AT</td> </tr> <tr> <td>763/99</td> <td>29 April 1999 (29.04.99)</td> <td>AT</td> </tr> <tr> <td>800/99</td> <td>5 May 1999 (05.05.99)</td> <td>AT</td> </tr> <tr> <td>1042/99</td> <td>14 June 1999 (14.06.99)</td> <td>AT</td> </tr> </table> <p>(71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT M B H [AT/AT]; A-6250 Kundl (AT).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GERLACH, Benjamin [DE/AT]; Dorf Nr. 411, A-6252 Breitenbach (AT). LUDESCHER, Johannes [AT/AT]; Kleinsöll 101, A-6252 Breitenbach (AT). TOTSCHNIG, Klaus [AT/AT]; Biochemies-trasse 44/4, A-6250 Kundl (AT).</p> <p>(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).</p>		673/99	15 April 1999 (15.04.99)	AT	763/99	29 April 1999 (29.04.99)	AT	800/99	5 May 1999 (05.05.99)	AT	1042/99	14 June 1999 (14.06.99)	AT	<p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
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<p>(54) Title: BETA-LACTAM PRODUCTION</p> <div style="text-align: center; margin: 20px 0;">  <p>(1 Abstract)</p> </div> <p>(57) Abstract</p> <p>The present invention provides processes for the production of a compound of formula (I_{Abstract}) wherein X, R₁ and R₂ are substituents conventional in cephalosporin chemistry; especially a compound of formula (I_{Abstract}) is ceftriaxone, cefotaxime; e.g. in the form of a salt.</p>														

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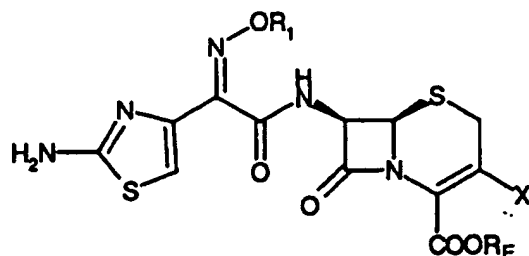
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Beta-lactam production

The present invention relates to the production of β -lactams, such as pharmaceutically active β -lactams, e.g. cephalosporins, such as ceftriaxone or similar compounds.

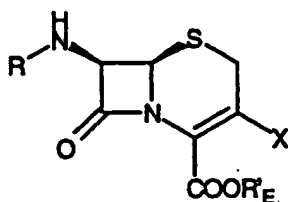
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In one aspect the present invention provides a process for the production of a compound of formula



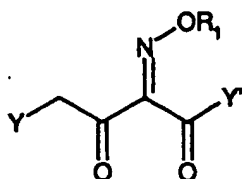
10 wherein X and R₁ are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO- group to which R_E is attached is an ester, e.g. ceftriaxone or cefotaxime; comprising

i) reacting a compound of formula



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wherein R is hydrogen or silyl, R'_E is silyl or together with the COO- group to which R'_E is attached is an ester, and X is as defined above, with a compound of formula

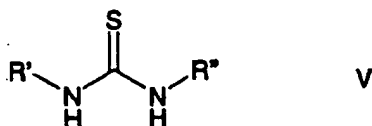


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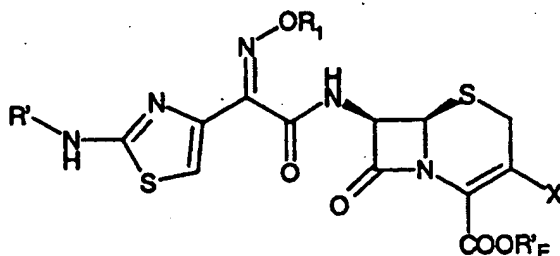
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R₁ is as defined above, to obtain a compound of formula



ii) reacting a compound of formula II wherein X, Y, R'_E and R₁ are as defined above, with a compound of formula



wherein R' is hydrogen or silyl and R'' is silyl; to obtain a compound of formula



VI

10

ii)

15

20

with a compound of formula V wherein R' and R'' are as defined above according to step ii) as defined above; or

desilylating a compound of formula II, wherein Y, X, R'E and R₁ are as defined above, and reacting a desilylated compound of formula II with thiourea according to step ii') as defined

5 above, to obtain a compound of formula I;

e.g. a compound of formula I in free form; e.g. or a compound of formula I in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt, and in the form of a solvate.

10 A compound of formula I in free form, in the form of an ester and in the form of a salt; e.g. and in the form of a solvate; e.g. or in the form of a non-solvate, may be obtained.

A compound of formula I in free form, e.g. and in the form of a solvate or in the form of a non-solvate; may be converted in the form of an ester or in the form of a salt; e.g. and in the form of a solvate, or in the form of a non-solvate; and vice versa. A compound of formula I in the

15 form of a solvate may be converted into a compound of formula I in the form of a non-solvate and vice versa. Conversion may be carried out according to a method as conventional, e.g. including a method as conventional.

It is one advantage of the present invention that a compound of formula II needs not to be
20 isolated in the course of the reaction. It is another advantage of the present invention that a process of the present invention may be a one-pot process.

In a compound of formula I,

X is a substituent useful in cephalosporin chemistry. A substituent useful in cephalosporin
25 chemistry includes e.g. a substituent according to a substituent conventional in cephalosporin chemistry, e.g. including a substituent conventional in cephalosporin chemistry. A substituent useful in cephalosporin chemistry includes a substituent which is useful in pharmaceutically active cephalosporins; and a substituent which is useful in intermediates for the production of pharmaceutically active cephalosporins. Preferably X is alkyl or alkenyl, more preferably
30 methyl or ethenyl; e.g. including unsubstituted or substituted alkyl and alkenyl; e.g. unsubstituted alkyl and alkenyl, and alkyl and alkenyl substituted by alkoxy, heterocyclythio, heterocyclylcarbonylthio; alkylcarbonyloxy, preferably methylcarbonyloxy; heterocyclyl;

R_1 is a substituent useful in cephalosporin chemistry. Preferably R_1 is unsubstituted or substituted alkyl, e.g. unsubstituted alkyl, or alkyl substituted by carboxyl. More preferably R_1 is methyl; carboxymethyl; or a group of formula $-C(CH_3)_2COOH$.

5 R_E is hydrogen, a negative charge or is, together with the COO^- group to which R_E is attached, an ester group; e.g. an ester group useful in cephalosporin chemistry.

If R_E is a negative charge, the group X may contain a positive charge; e.g. in the form of a positively charged amine.

10 If R_E together with the COO^- group to which R_E is attached is an ester group R_E preferably forms with the COO^- group a physiologically hydrolysable and acceptable ester; e.g. R_E is a substituent useful in cephalosporin chemistry.

A compound of formula I may thus be in the form of a physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO^- group together with R_E forms an ester which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term " R_E together with the COO^- group to which R_E is attached is an

15 ~~ester group~~ is thus to be understood as defining regular pro-drug forms of a compound of formula I. A group $-OR_E$ may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally, since hydrolysis usually takes place under the influence of the digestive enzymes. Parenteral administration may be indicated if the ester per se is an active compound or, if hydrolysis occurs in the blood.

If not otherwise defined herein heterocyclyl includes e.g. 5 or 6 membered heterocyclyl; e.g. including a bicyclic ring system, e.g. of 10 to 12 carbon atoms; e.g. heterocyclyl having 1 to 4
25 heteroatoms; e.g. selected from N, O or S; e.g. including unsubstituted heterocyclyl or substituted heterocyclyl, e.g. unsubstituted heterocyclyl or heterocyclyl substituted; e.g. by one or more substituents; e.g. by a substituent useful in cephalosporin chemistry; e.g. heterocyclyl substituted by alkyl, e.g. including (C_{1-4}) alkyl; carboxyalkyl; carbonyl. Alkyl includes (C_{1-4}) alkyl. Alkenyl includes (C_{2-4}) alkenyl. Alkoxy includes (C_{1-4}) alkoxy. Silyl includes trialkylsilyl, e.g.
30 trimethylsilyl. Halogen (halo-) includes bromide, chloride, iodide.

A solvent system or solvent (system) includes one or more individual solvents.

Preferably a compound of formula I is cefdinir (see e.g. Merck Index, 12th edition, item 1971), cefditoren (see e.g. Merck Index, 12th edition, item 1972), cefepime (see e.g. Merck Index, 12th edition, item 1973), cefetamet (see e.g. Merck Index, 12th edition, item 1974), cefixime (see e.g. Merck Index, 12th edition, item 1975); cefmenoxime (see e.g. Merck Index, 12th edition, item 1976), cefodizime (see e.g. Merck Index, 12th edition, item 1979), cefotaxime (see e.g. Merck Index, 12th edition, item 1983), cefpirome (see e.g. Merck Index, 12th edition, item 1990), cefpodoxime and cefpodoxime proxetil (see e.g. Merck Index, 12th edition, item 1991), ceftazidime (see e.g. Merck Index, 12th edition, item 191995), ceftoram (see e.g. Merck Index, 12th edition, item 1996), ceftiofur (see e.g. Merck Index, 12th edition, item 1999), ceftriaxone (see e.g. Merck Index, 12th edition, item 2001), cefuzonam (see e.g. Merck Index, 12th edition, item 2003); more preferably a compound of formula I is ceftriaxone or cefotaxim.

A compound of formula I includes a compound of formula I in free form, in the form of an ester and in the form of a salt; e.g. and in the form of a solvate or in the form of a non-solvate.

15

Step i) may e.g. be carried out as follows:

Compounds of formulae III and IV are known and may be prepared according to a method as conventional. In a compound of formula III, Y' is a group which forms a basis that a compound of formula III is in a reactive form; e.g. including halogen, a group which forms together with the -C=O group to which Y' is attached an active ester, and a group which forms together with the

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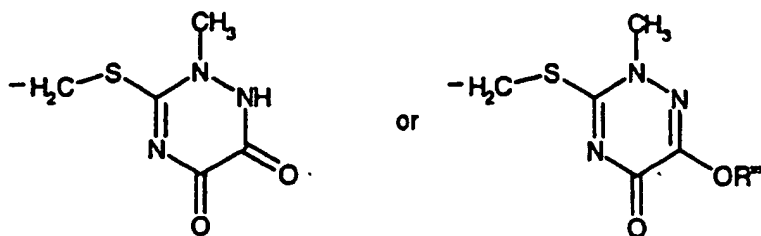
-C=O group to which Y' is attached a mixed anhydride.

If X and/or R₁ comprise silylatable groups (functions), such groups may be in silylated form in a compound of formulae II, IV and VI. If X and/or R₁ comprise silylated groups in a compound of formulae II or VI such groups are desilylated in step ii) or ii'). Preferably a compound of formula II or of formula VI contains one or more silyl groups.

25

In another aspect the present invention provides a compound of formula II wherein R'_E, R₁ and Y are as defined above; e.g. a compound of formula II, wherein preferably R'_E is silyl, R₁ is methyl and Y is defined as above; and X denotes a group of formula

30



wherein R''' is silyl.

Such compounds are new; are e.g. useful intermediates, e.g. in the production of pharmaceutically active cephalosporins; e.g. and may be obtained by reaction of a compound of formula III, wherein Y is halogen, e.g. bromo, chloro; and Y' is halogen, e.g. chloro; with a compound of formula IV wherein R'E is silyl, and X is one of the above two mentioned groups; e.g. in an organic solvent (system).

Step II) may be carried out as follows:

Thiourea may be silylated with a silylation agent in a solvent (system) inert under the reaction conditions. Appropriate silylation agent e.g. includes silylation agents according to conventional silylation agents, e.g. including conventional silylation agents, e.g. mono- or bis-silylated amides, e.g. derived from formamides, acetamides or trifluoroacetamides; bis-(trimethylsilyl)-urea or hexamethyldisilazane, e.g. in combination with an acid; halosilanes, e.g. chlorosilanes, e.g. in combination with an acid acceptor, e.g. an amine, such as triethylamine, tert.octylamine. A solvent (system) includes e.g. halogenated, e.g. chlorinated, hydrocarbons, such as dichloromethane; esters, e.g. ethyl acetate; and ethers; e.g. tetrahydrofuran. A compound of formula V, wherein R' and R'' are as defined above, may be obtained.

20

In another aspect the present invention provides a compound of formula V, wherein R' is hydrogen or tri(C₁₋₄)alkylsilyl, e.g. trimethylsilyl; and R'' is tri(C₁₋₄)alkylsilyl; e.g. trimethylsilyl.

Compounds of formula V are useful intermediates, e.g. in the production of pharmaceutically active cephalosporins. If an equivalent amount or more of a silylation agent is used in respect with the two possible reaction sites in thiourea, a compound wherein both, R' and R'', are tri(C₁₋₄)alkylsilyl may be obtained. If an amount below the equivalent amount is used in respect with the two possible reaction sites in thiourea, e.g. an amount equivalent in respect with one

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of the possible reaction sites in thiourea, a compound of formula V may be obtained wherein R' is hydrogen and R'' is tri(C₁₋₄)alkylsilyl.

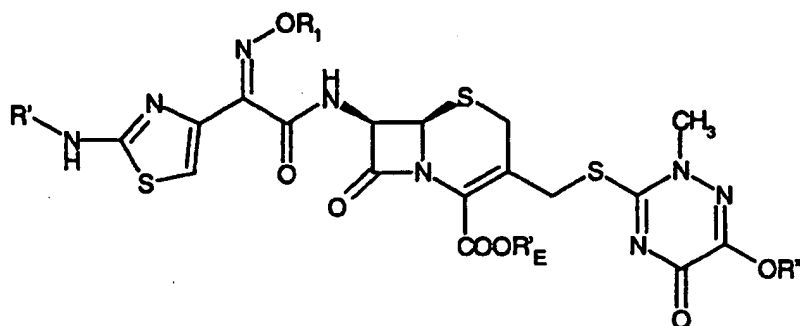
A compound of formula V may be obtained in the form of a mixture of a compound of formula V wherein R' is hydrogen and R'' is tri(C₁₋₄)alkylsilyl and a compound of formula V wherein

5 both, R' and R'', are tri(C₁₋₄)alkylsilyl. A compound of formula V may be isolated, e.g. according to a method as conventional. In a reaction according to the present invention a compound of formula V is preferably not isolated.

E.g. according to step ii) a compound of formula II wherein R'_E, R₁, X and Y are as defined
10 above; e.g. wherein in a group X and /or in a group R₁ silyl groups may be present; may be reacted with a compound of formula V, wherein R' and R'' are as defined above, e.g. produced as described above or in the examples. That reaction may be carried out in a solvent (system), e.g. a solvent (system) as described above in the production of a compound of formula V. An acid acceptor may be present, e.g. to bind an acid, e.g. formed in the course of the reaction;
15 e.g. including mono- or bis-silylated amides, e.g. as described above; or amines, e.g. trialkylamines, such as N,N-diisopropylethylamine.

A compound of formula VI wherein R'_E is as defined above; e.g. wherein in a group X and/or R₁ silyl groups may be present; may be obtained.

20 In another aspect the present invention provides a compound of formula



e.g. which is a compound of formula VI; wherein R₁ is as defined above, e.g. methyl; and R',
25 R'_E and R'' are tri(C₁₋₄)alkylsilyl, e.g. trimethylsilyl; e.g. useful in the production of ceftriaxone, e.g. or similar compounds.

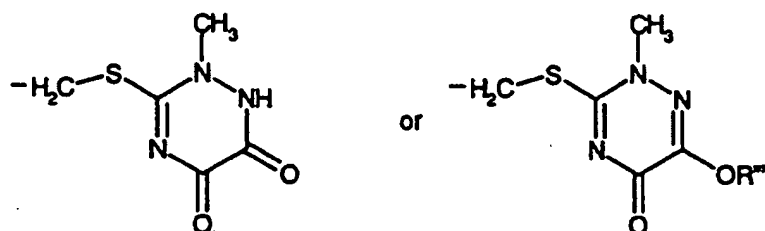
Desilylation of a compound of formula VI obtained in a process according to the present invention may be e.g. either carried out according to a method as conventional, e.g. by treatment with an alcohol and/or water and isolating a compound of formula I obtained; or may be carried out in the course of the isolation of a compound of formula I; e.g. a compound of formula I may directly be isolated from the reaction mixture containing a compound of formula VI comprising silyl groups, in free form, in the form of an ester or the form of a salt, and e.g. in the form of a solvate or in the form of a non-solvate; e.g. without isolating a compound of formula VI. This may be carried out e.g. according to a method as conventional; e.g. using appropriate extraction and isolation steps, such as:

- 10 E.g. Completing desilylation before isolating a compound of formula I;
e.g. Choosing optimal pH conditions in respect with stability and isolation of a compound of formula I, e.g. by use of buffer solutions, alkaline solutions or ammonium salt solutions of organic acids such as carbonates, carboxylates, phosphates, phosphonates and borates;
e.g. Choosing optimal conditions in respect with the solubility of a compound of formula I,
15 e.g. Choosing optimal solvent (system) conditions; e.g. beside water, organic solvents may be used, e.g. alcohols, such as (C₁₋₄)-alcohols, such as 2-propanol; ketones, e.g. acetone; nitriles, e.g. acetonitrile; esters, e.g. methyl acetate; ethers, e.g. tetrahydrofuran; and amides, e.g. dimethylformamide;
e.g. Choosing an aqueous/organic solvent system which may optimize the separation of side
20 products.

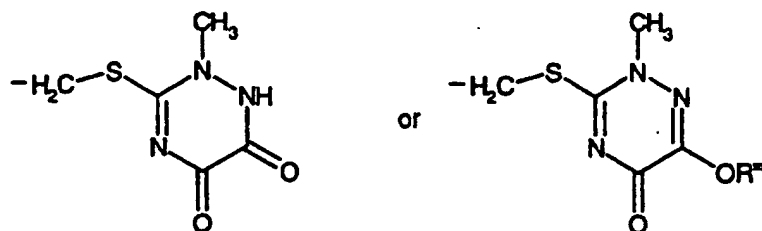
- E.g. ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate, may be directly obtained from a reaction mixture containing a corresponding silylated ceftriaxone of formula VI, e.g. by treating the reaction mixture containing a silylated
25 ceftriaxone, e.g. produced according to a process of the present invention, with a mixture of water and organic solvent which is miscible with water, e.g. acetone; and a base, e.g. a sodium source; e.g. sodium 2-ethylhexanoate; and with a mixture of water and an organic solvent which is able to form a two-phase system with water, e.g. dichloromethane. The pH of the mixture obtained is adjusted to about 6.5, e.g. 6.5; by addition of a base, e.g. sodium
30 bicarbonate. A two-phase system is formed. The organic phase is separated off and the pH of the aqueous phase is adjusted to a pH of about 3, e.g. 3; by addition of an acid, e.g. hydrochloric acid. A precipitate (ceftriaxone in free form) is obtained and filtrated off. The precipitate obtained is suspended in a mixture of water and organic solvent which is miscible

with water, e.g. acetone; and the pH of the mixture obtained is adjusted to about 6.5, e.g. 6.5; by addition of a sodium source, e.g. a sodium salt, e.g. sodium bicarbonate. A solution is obtained from which ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate; crystallizes and may be isolated, e.g. by filtration. E.g. by addition of further
 5 organic solvent, e.g. acetone; crystallization may be completed.

In another aspect the present invention provides a process for the production of ceftriaxone in the form of a disodium salt, e.g. and in the form of a hemiheptahydrate; e.g. in high purity; e.g. in crystalline form; comprising reacting a compound of formula II wherein Y is as defined
 10 above, R_1 is CH_3 , R'_E is silyl; and X is a group of formula



wherein R'' is as defined above, with a compound of formula V, wherein R' and R'' are as
 15 defined above to obtain a compound of formula VI, wherein R'_E is silyl; R_1 is CH_3 , R' is as defined above and X is a group of formula



- wherein R'' is as defined above; and
- 20 i) treating the reaction mixture obtained with water/organic solvent which is miscible with water, a base and with water/organic solvent which is able to form a two-phase system with water;
- ii) adjusting the pH of the mixture obtained to about 6.5; e.g. by addition of a base;
- iii) separating off the organic solvent from the two-phase system obtained;

- iv) adjusting the pH of the aqueous phase obtained to a pH of about 3; e.g. by addition of an acid,
- v) filtrating off the precipitate formed;
- vi) suspending the precipitate obtained in a mixture of water and organic solvent which is miscible with water;
- vii) adjusting the pH of the mixture obtained to about 6.5; e.g. by addition of a base; e.g. and adding acetone to the mixture obtained to complete crystallisation; and
- viii) isolating ceftriaxone in the form of a disodium salt; e.g. and in the form of the hemiheptahydrate.

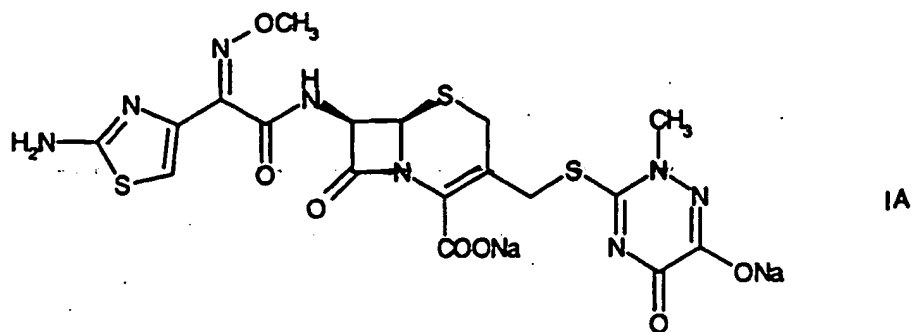
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A process for the production of ceftriaxone in the form of a disodium salt according to the present invention may be e.g. carried out as follows:

- A compound of formula II wherein R'_E , R_1 , X and Y are as described above, e.g. obtained as described above; is desilylated, e.g. according to a method as conventional, e.g. by treatment with alcohol and/or water. A compound of formula II which is desilylated may be obtained and may be reacted, e.g. without isolation from the reaction mixture obtained; with thiourea in a solvent mixture (system) comprising water; e.g. in organic solvent, e.g. a solvent which is able to form a two-phase system with water, including halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane, esters, e.g. acetic acid (C_{1-4})alkyl esters; ethers, e.g. diisopropylethers; and in the presence of water; and e.g. in the presence of alcohols, such as an (C_{1-4})alcohol, e.g. ethanol or isopropanol. Preferably an alcohol is present, e.g. in an appropriate amount; e.g. including amounts of 5% to the double volume of the volume of the total solvent system used, e.g. in case of dichloromethane present as an organic solvent, including amounts of 5% to 30 % of the volume of the total solvent system used. A base, e.g. an amine, e.g. triethylamine, may be present; e.g. in order to neutralize an halogenic acid set free in the course of the reaction. A compound of formula I may be obtained; e.g. in free form or in the form of a salt; and e.g. in the form of a solvate or in the form of a non-solvate; and may be isolated and e.g. may be purified; e.g. according to a method as conventional; e.g. or according to a method as described above.

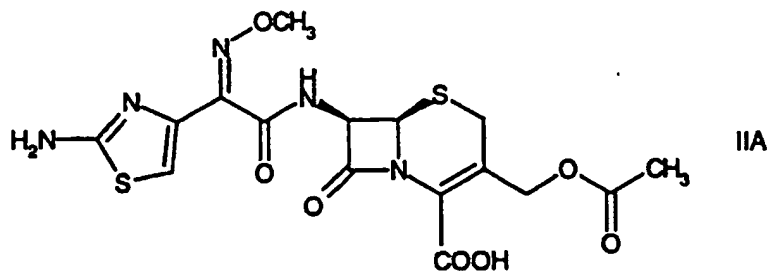
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In another aspect the present invention provides a process for the production of ceftriaxone in the form of a disodium salt, e.g. of formula

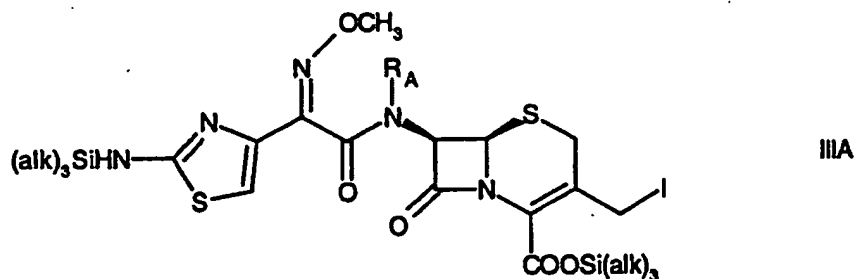


comprising

i) silylating a compound of formula



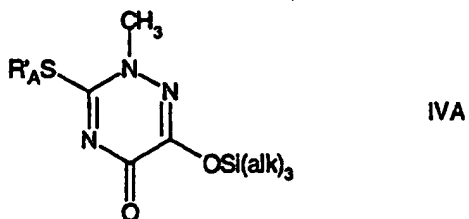
5 or a compound of formula IIA in the form of a salt and iodinating; e.g. a compound obtained in silylation; to obtain a compound of formula



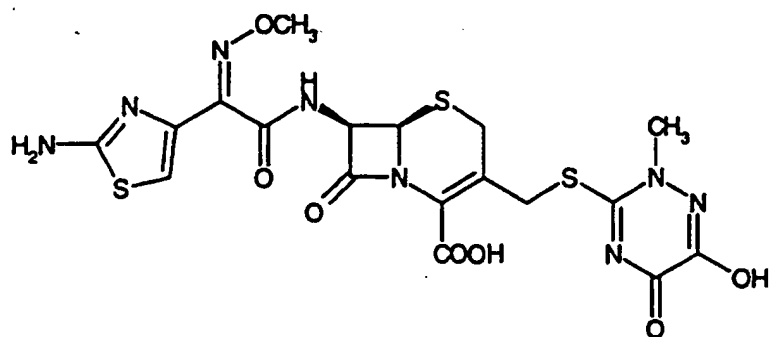
wherein R_A is hydrogen or trialkylsilyl; e.g. trimethylsilyl; and alk is alkyl, e.g. methyl;

ii) reacting a compound of formula IIIA obtained in step i) with a compound of formula

10



wherein R'_A is hydrogen or trialkylsilyl, e.g. trimethylsilyl; and desilylating; e.g. a compound obtained by reaction of a compound of formula IIIA with a compound of formula IVA₁, to obtain a compound of formula



VA

- 5 iii) isolating a compound of formula VA obtained in step ii) from the reaction mixture; and
- iv) converting a compound of formula VA obtained in step iii) into ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate.

10 A process for the production of a compound of formula VA according to the present invention may be carried out as follows:

Step i) may be carried out according to a method as conventional and is preferably carried out as follows:

15 In step i) a compound of formula IIIA may be obtained by treating a compound of formula IIA (e.g. the compound 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyloxy) methyl-3-cephem-4-carboxylic acid, i.e. cefotaxime in free form) or a compound of formula IIA in the form of a salt; e.g. in the form of an ammonium salt; or in the form of a sodium salt (sodium cefotaxime); preferably sodium cefotaxime; with a silylation agent and an iodination agent in a solvent (system).

20 Preferably sodium cefotaxime is used, e.g. in view of the fact, that

- cefotaxime in free form is a strongly solvating molecule, e.g. acetone and ethanol solvates of cefotaxime are known;
- cefotaxime in free form may contain considerable amounts of water;

whereas sodium cefotaxime is poorly solvating and contains usually less amounts of solvent than cefotaxime in free form. Thus, if sodium cefotaxime is used instead of cefotaxime in free

25 form, less silylation agent, e.g. trialkylsilylation; agent which may be reactive in respect with solvent (system), e.g. water and acetone, may be used.

Appropriate silylation agents include silylation agents usable according to conventional silylation processes; e.g. halosilanes, such as iodotrialkylsilane, e.g. iodotrimethylsilane (TMIS), e.g. in the presence of a nucleophile base; silylated amides, e.g. N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA); N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA);

5 silazanes, e.g. 1,1,3,3,3-hexamethyldisilazane (HMDS); silylated ureas, such as bis-(trimethylsilyl)-urea (BSS), N,N'-bis-(trimethylsilyl)-urea (BSU); or a mixture of two or more of silylation agents; e.g.; a mixture of BSTFA or MSTFA or BSS or BSU with HMDS; preferably a mixture of BSTFA or MSTFA or BSS or HMDS with TMIS. The choice of a specific silylation agent may be important to

10 enhance e.g. yield and purity of a desired compound of formula IIIA. If sodium cefotaxime is used for silylation preferably BSTFA, BSS or HMDS in combination with TMIS may be used. If cefotaxime in free form is used for silylation preferably HMDS, e.g. in the presence of a silylation catalyst, e.g. including a silylation catalyst according to a conventional process; may be used. Preferably silylation is carried out before iodination.

15 An iodination agent includes an iodination agent usable in iodination reactions, e.g. according to a conventional iodination reaction, e.g. an iodination agent conventional in cephalosporin chemistry, e.g. an iodotrialkylsilane, preferably TMIS, e.g. produced in situ from iodine and hexamethyldisilane in dichloromethane. Preferably per mol of cefotaxime in free form or in the form of a salt 1.5 to 2.5 mol of iodination agent may be used. Iodination may be completed

20 after silylation, e.g. a first amount of TMIS may be added to a compound of formula IIA preferably for silylation; and a second amount thereafter may be added for completing iodination.

To obtain a compound of formula IIIA wherein R'_A denotes trialkylsilyl, e.g. after iodination, a corresponding higher amount of a silylation agent may be used than for the case where R'_A

25 denotes hydrogen.

An appropriate solvent (system) includes a solvent (system) inert under the reaction conditions, e.g. halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane; nitriles; preferably dichloromethane.

A compound of formula IIIA obtained via silylation and iodination of a compound of formula IIA

30 may be isolated, e.g. according to a process as conventional; but is preferably further reacted without isolation with a compound of formula IVA.

In step ii) a compound of formula IIIA ; e.g. as obtained in step i); is reacted with a compound of formula IVA, e.g. silylated 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin; e.g. to obtain a compound of formula VA in a silylated form; and desilylating a compound of formula VA in a silylated form, to obtain a compound of formula VA; e.g. 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]-3-cephem-4-carboxylic acid; in a solvent (system). Step ii) may be carried out according to a method as conventional and preferably may be effected as follows:

A compound of formula IVA which contains silylatable oxygen functions and which has a better solubility, e.g. in organic solvent (system); in a silylated form than in a non-silylated form, may be obtained by silylation of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin. Appropriate silylation agents include e.g. silylated amides; such as N,O-bis-(trimethylsilyl)-acetamide (BSA), N-methyl-N-trimethylsilyl-acetamide (MSA), BSS, BSU; or a silylation agent as appropriate in step i) for silylating a compound of formula IIA; of the present invention; preferably BSA. An appropriate solvent (system) includes solvent (system) inert under the reaction conditions, e.g. halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane; nitriles, e.g. acetonitrile; amides, e.g. dimethylacetamide; esters, e.g. ethylacetate; and ethers, e.g. tetrahydrofuran; preferably dichloromethane. BSA as a silylation agent together with dichloromethane as a solvent are preferred; e.g. in view of the finding of a quick silylation and easy solvent recovery.

Per mol of a compound of formula IIIA about 1 mol of a compound of formula IVA; e.g. or more; may be used. Preferably per mol of of a compound of formula IIA, or of a compound of formula IIA in the form of a sodium salt 0.9 to 1.1 of a compound of formula VIA may be appropriate.

A compound of formula VA may be obtained which is isolated according to step iii) of the present invention.

Preferably steps i) and ii) may be carried out as follows:

Sodium cefotaxim in dichloromethane is silylated with a mixture of BSTFA or BSS with TMIS. 1.5 to 2.5 mol per mol of sodium cefotaxime are added to the reaction mixture obtained in silylation at appropriate temperatures, e.g. at a temperature from -20° to 20°C; preferably from 0° bis 10 °. A compound of formula IIIA is obtained and is reacted with a compound of formula IV, produced by reaction of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin with BSA in dichloromethane. A compound of formula VA in a silylated form may be obtained.

Desilylation of a compound of formula VA in a silylated form may be carried out according to a method as conventional, e.g. by treatment with water and/or alcohol, e.g. in the presence of organic solvent (system); e.g. solvent originating from the reaction of a compound of formula IIIA with a compound of formula IVA; and e.g. in the presence of a base, preferably sodium acetate or an amine. More preferably a reaction mixture obtained in step ii) is mixed with an alcoholic solution of sodium acetate and water. A compound of formula VA may be obtained.

Step iii), i.e. isolation of a compound of formula VA, may be effected according to a method as conventional and is preferably effected as follows:

- 10 The pH of a reaction mixture obtained in step ii) may be adjusted to (about) 4 to 7, preferably to (about) 6 to 6.5, e.g. either after desilylation of a compound of formula VA in a silylated form; or during desilylation, e.g. in case that a base is used in the desilylation step; preferably after desilylation. A reducing agent may be added to the reaction mixture, e.g. in order to remove reduceable components present in the reaction mixture, e.g. iodine; e.g. including
- 15 thiosulphate, bisulfite, ascorbinic acid. Water and an organic solvent, which is able to form a two-phase system with water, e.g. dichloromethane, is added to the mixture obtained and a two-phase system is formed. The phases are separated and the organic phase is dismissed. In order to remove colored impurities the aqueous phase may be treated with charcoal. After charcoal removal, the pH of the aqueous phase may be adjusted to (about) 2.0 to 3.5, e.g. 3.0.
- 20 A compound of formula VA may precipitate and may be isolated, e.g. by filtration.

- According to conventional methods in ceftriaxone production a compound of formula VA is usually not isolated from a reaction mixture containing it, but isolated in the form of a salt, e.g. directly as a compound of formula IA; or in the form of another salt, e.g. in the form of a
- 25 dibenzylethyldiamine salt. We have found that isolation of a compound of formula VA according to the present invention surprisingly may improve the quality, e.g. purity, side product-profile (e.g. less side products), content, color, and may improve surprisingly the crystallisation behaviour, of a compound of formula IA, produced from an isolated compound of formula VA, e.g. compared with direct production of a compound of formula IA from a
- 30 compound of formula VA without isolation of a compound of formula VA.

According to step iv) a compound of formula VA isolated in step iii) is converted into a compound of formula IA, e.g. ceftriaxone in the form of a disodium salt. Step iv) may e.g. be carried out according to a conventional method and is preferably carried out as follows:

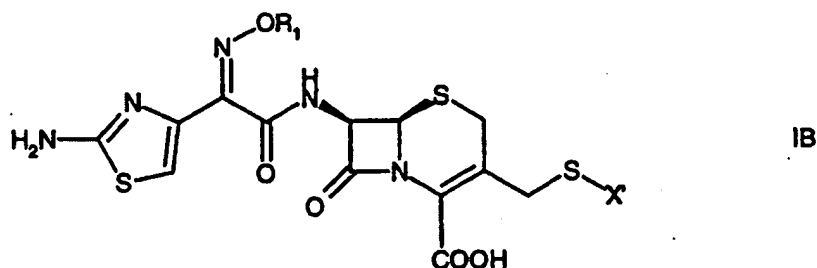
5 Preferably a compound of formula VA in isolated form, e.g. isolated as described in step iii), is further purified before conversion into a compound of formula IA. Further purification includes e.g. dissolution in an alcohol, e.g. methanol and charcoal treatment of the mixture obtained.

For conversion a compound of formula VA is treated in a solvent (system) with a sodium source to obtain a pH of the mixture of (about) 5.0 to 7.0. A solvent (system) includes a mixture of organic solvent, preferably acetone; and water, e.g. in a range of organic

10 solvent:water of e.g. 1:1 to 10:1; such as 3:1 to 8:1; e.g. 5:1. A sodium source includes e.g. a sodium salt, e.g. a sodium salt of an acid, e.g. sodium hydroxide, carbonate, bicarbonate, acetate. Ceftriaxone in the form of a disodium salt, e.g. in the form of a hemiheptahydrate; may crystallize. Crystallization may be completed by addition of organic solvent, e.g. by addition of further acetone.

15 A compound of formula IA, i.e. ceftriaxone in the form of a disodium salt may be obtained and may be isolated in surprising high purity.

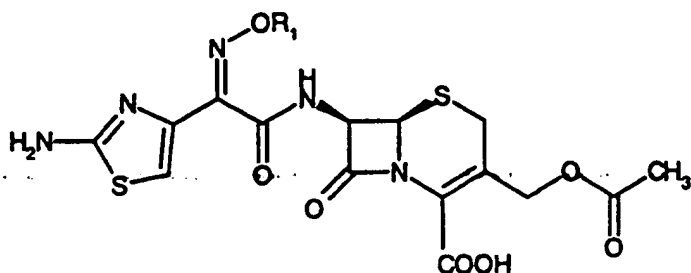
In another aspect the present invention provides a process for the production of a compound of formula



20 wherein X' and R₁ are substituents useful in cephalosporin chemistry; e.g. a compound of formula I is ceftriaxone; e.g. in free form, in the form of an ester or in the form of a salt; e.g. and in the form of a solvate; or in the form of a non-solvate;

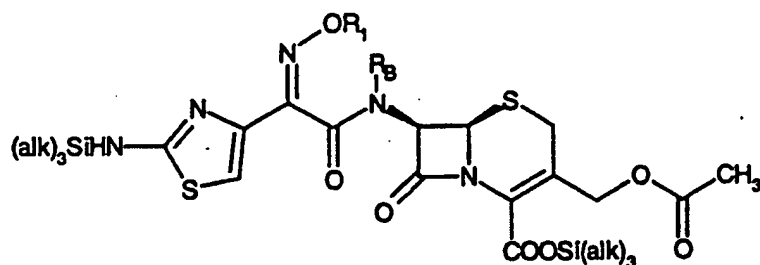
25 comprising

i) silylating a compound of formula



IIB

or a compound of formula IIB in the form of a salt, to obtain a compound of formula



IIIB

5

wherein R_B is hydrogen or trialkylsilyl, and alk is alkyl;

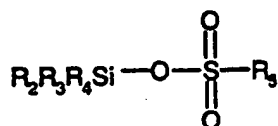
ii) reacting a compound of formula IIIB with a compound of formula

10



IVB

wherein R'_B is hydrogen or trialkylsilyl and X' is as defined above, in the presence of a compound of formula



VB

15

wherein R_2 , R_3 and R_4 independently of each other are aryl or alkyl, and R_5 is alkyl or aryl; e.g. trimethylsilyl-trifluoromethanesulfonate; and

iii) isolating a compound of formula IB from the reaction mixture obtained in step ii).

20

In a compound of formula IB, X' and R_1 are substituents useful in cephalosporin chemistry; e.g. R_1 is alkyl, e.g. methyl; and X' is heterocyclyl or heterocyclcarbonyl, preferably heterocyclyl. A compound of formula IB is preferably ceftriaxone.

A compound of formula IIB is e.g. 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyloxy)methyl-3-cephem-4-carboxylic acid (cefotaxime in free form). A compound of formula II may be in free form or in the form of a salt, e.g. an ammonium salt or a sodium salt, preferably in the form of a sodium salt (sodium cefotaxime).

5 In process step i) a compound of formula IIB is silylated with a silylation agent to obtain a compound of formula IIIB. Process step i) may e.g. be carried out according to a method as conventional. A preferred silylation agent includes e.g.

- if a compound of formula II is used (cefotaxime in free form) preferably HMDS, BSTFA, MSTFA, e.g. in any combination;

10 - if a compound of formula IIB is used in the form of the sodium salt (sodium cefotaxime) preferably BSS, BSTFA, HMDS, e.g. in the presence of a halotrialkylsilane, such as trimethylchlorosilan (TMCS).

Appropriate solvent (system) in the production of a compound of formula IB in a silylated form according to the present invention include preferably solvent (system) which may
15 advantageously be used in all reaction steps i) to ii); e.g. solvent (system) which is inert during the whole reaction sequence; e.g. and which is compatible under the reaction conditions.

Appropriate solvent (system) includes halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane, aliphatic and aromatic hydrocarbons, e.g. cyclohexane, toluene; nitriles, e.g. acetonitrile, e.g. including mixtures of individual solvents as mentioned above; preferably
20 dichloromethane, cyclohexane; toluene.

A compound of formula IIIB may be obtained and may be isolated from the reaction mixture, e.g. according to a method as conventional; a compound of formula IIIB is preferably not isolated from the reaction mixture but further reacted in step ii).

25 Process step ii) may be carried out as follows:

A compound of formula IIIB is reacted with a compound of formula IVB in the presence of a compound of formula VB.

A compound of formula IVB may be obtained by silylation of a compound of formula IVB which is in a non-silylated form. Compounds of formula IVB and compounds of IVB in a non-silylated
30 form are known or may be prepared e.g. according to a method as conventional. Silylation of a compound of formula IV in a non-silylated form may e.g. be carried out according to a method as conventional. The group X' in a compound of formula IVB may comprise silylatable functions which are preferably silylated in the course of silylation of a compound of formula

IVB. Preferred solvents include solvent as described in step i) above. Preferred silylation agents include e.g. HMDS, BSU, 2-trimethylsilyl-1-oxazolidinone (TMSO), TMCS, e.g. in the presence of a base; BSTFA, BSA; preferably BSTFA, which is highly reactive in the silylation of the thiol function and other silylatable functions, e.g. as present in a group X'.

- 5 Compounds of formula VB are known or may e.g. be prepared according to a method as conventional. The choice of a specific compound of formula VB may be dependent on the reactivity and availability of a compound of formula VB. E.g. trialkylsilyl-sulfonic acid esters; trimethylsilyl-trifluoromethanesulfonate (TMSTf), t-butyl-dimethylsilyl-trifluoromethanesulfonate, trimethylsilyl-nonafluorobutanesulfonate, trimethylsilyl-methanesulfonate or trimethylsilyl-
10 benzenesulfonate are commercially available.

- Preferred compounds of formula VB include compounds of formula VB, wherein R_2 , R_3 and R_4 independently of each another are aryl or alkyl, preferably alkyl; and R_5 is alkyl, preferably perfluorinated alkyl, e.g. $-CF_3$. Preferably R_5 is a strong electron withdrawing (electrophilic) substituent, e.g. perfluorinated alkyl; e.g. perfluorinated sulfonates; e.g. trifluorosulfonate; or
15 aryl, carrying substituents which are strong electron withdrawing (electrophilic) substituents; e.g. perfluorinated alkyl, perfluorinated sulfonates, e.g. methanesulfonates; nitro groups. A preferred compound of formula VB is trimethylsilyl-trifluoromethanesulfonate.

- A compound of formula IIIB and a compound of formula IVB, e.g. commonly silylated in one
20 pot; may be treated in a solvent (system); e.g. as described above; with a compound of formula VB; to obtain a compound of formula IB in a silylated form.

According to the present invention there are involved several silylation steps. In respect with silylation agents the following comments may be of interest:

- 25 The choice of the silylation agent may influence the reaction e.g. in view of the different silylated compounds which are used. E.g. a compound of formula VB is a strong silylation agent itself and may thus silylate silylatable functions in molecules involved in the reaction sequence in the production of a compound of formula IB in a silylated form according to the present invention. In order to minimize the necessary amount of a compound of formula VB, it
30 may be advantageous to achieve high silylation grades; i.e. silylation as complete as possible; in the production of a compound of formulae IIIB and IVB; although the reaction according to the present invention also works if compounds of formulae IIIB and IVB are incompletely silylated; e.g. if correspondingly the amount of a compound of formula VB is enhanced.

It is also advantageous to use such silylation agents in the silylation of a compound of formula IIIB and/or IVB, which; or which metabolites thereof obtained after reaction; do not disturb the function of a compound of formula VB, e.g. by reaction with a compound of formula VB; e.g. which do not react with a compound of formula VB.

- 5 As already described above it should also be considered that the choice of a highly appropriate silylation agent may be dependent, whether a compound of formula IIB is used as such or in the form of a salt.

X' in a compound of formula IIB may further contain silylatable functions, which preferably should be already in a silylated form, e.g. as complete as possible, before a compound of
10 formula VB is added to the reaction mixture.

The process of the present invention may be carried out e.g. in a one-pot reaction; e.g. a compound of formula IIB and a compound of formula IVB may be silylated commonly and may be reacted in the same pot with a compound of formula VB, e.g. to obtain a compound of formula IB in a silylated form.

- 15 Corresponding to the silylation grade achieved in a compound of formulae IIIB and IVB; including the silylation grade of a group X' comprising silylatable functions in a compound of formula IIIB; the necessary amount of a compound of formula VB may be determined and may be added in step ii) of the process of the present invention.

- 20 Process step iii) may be carried out according to a method as conventional and is preferably carried out as follows:

The reaction mixture obtained after reaction of the compounds of formulae IIIB with IVB in the presence of a compound of formula VB; e.g. to obtain a compound of formula IB in a silylated form; is treated in aqueous or alcoholic solvent system, e.g. in the presence of an organic
25 solvent; e.g. including neutralization of the reaction mixture with a base.

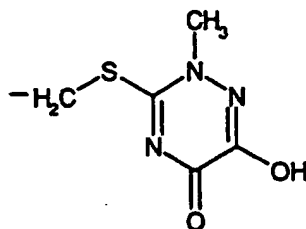
Preferably a desilylation step is carried out; e.g. according to a method as conventional in desilylation reactions. E.g. preferably a base is added, e.g. an alkali salt of a weak acid, e.g. sodium acetate; or an amine; to a reaction mixture obtained in step ii). The base may be dissolved in an alcohol, e.g. methanol; e.g. comprising water. A precipitate comprising a
30 compound of formula IB may be formed upon addition of the base.

E.g. a compound of formula IB may be directly isolated by isolation of the precipitate formed; or via extraction steps. For isolation via extraction steps water and an organic solvent which is able to form a two-phase system with water may be added to the mixture obtained by addition

of a base to a reaction mixture obtained in step ii). A two-phase system may be obtained and the pH of the mixture obtained may be adjusted and a compound of formula IB may be extracted into the aqueous phase. The aqueous phase may be purified by charcoal treatment. The pH of the aqueous phase may be adjusted to an acidic pH, e.g. an pH from 2.0 to 3.5 and
5 a compound of formula IB may precipitate and may be isolated according to a method as conventional.

A compound of formula IB may be isolated in free form, or in the form of a salt from the reaction mixture; e.g. and in the form of a solvate. A compound of formula IB in free form, optionally in the form of a solvate; may be converted in a compound of formula IB in the form
10 of a salt; preferably in the form of a pharmaceutically acceptable salt; e.g. and in the form of a solvate. Precipitation of a compound of formula IB in free form may also be circumvented, if desired. E.g. if a compound of formula IB in the form of a salt, e.g. a sodium salt, is desired to be isolated, a salt forming agent, e.g. including a sodium salt forming agent, e.g. sodium bicarbonate; may be added to an aqueous solution containing a compound of formula IB in
15 free form and a compound of formula IB in the form of a salt, e.g. and in the form of a solvate; may be isolated from the reaction mixture. Alternatively a compound of formula IB may be isolated from the reaction mixture and may be converted in the form of a salt after isolation.

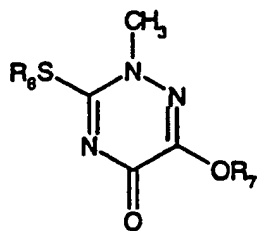
In a preferred embodiment of the present invention X' in a compound of formula IB denotes a
20 group of formula



e.g. a compound of formula IB is ceftriaxone.

Ceftriaxone is preferably produced as follows:

A suspension of sodium cefotaxime in dichloromethane is cooled and silylated with BSS; e.g. 2
25 to 4 moleequivalents BSS per mol of sodium cefotaxime (Solution A); e.g. to obtain a compound of formula III. A suspension of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in dichloromethane is silylated with BSTFA, e.g. 1 to 5 moleequivalents BSTFA per mol of sodium cefotaxime; to obtain a compound of formula VIIa or VIIb; or a mixture of a compounds of formula VIIa and VIIb:



VIIa: $R_6=H$, $R_7=Si(CH_3)_3$

VIIb: $R_6, R_7=Si(CH_3)_3$

(Solution B).

Solutions A and B are combined and 1 to 10 molequivalents of TMSTf are added per mol of sodium cefotaxime to the combined solutions.

Alternatively cefotaxime in free form and 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin are commonly silylated in dichloromethane and TMSTf is added; e.g. 1 to 10 molequivalents TMSTf per mol of cefotaxime in free form; to the mixture obtained.

The reaction mixture obtained is combined with an aqueous and/or alcoholic mixture of water and sodium acetate or triethylamine. A precipitate may be formed and either the precipitate comprising ceftriaxone is filtrated off and ceftriaxone is isolated in the form of a precipitate; or a solvent which is able to form a two-phase system with water, e.g. dichloromethane; is added to the mixture obtained upon addition of an aqueous and/or alcoholic mixture of water and sodium acetate or triethylamine. A two-phase system is obtained and ceftriaxone is extracted into the aqueous phase, e.g. after pH adjustment to 5 to 7, preferably to 6 to 6.5 by addition of a base, e.g. a sodium salt of a weak acid, e.g. sodium bicarbonate or sodium acetate. The phases are separated and the aqueous phase is purified by charcoal treatment. E.g. in order to separate off water soluble contents from ceftriaxone, the pH of the aqueous phase may be adjusted to 1.0 to 3.5, e.g. 3.0. Ceftriaxone in free form may precipitate and may be filtrated off.

Ceftriaxone obtained may be further purified by dissolution in an alcohol, e.g. methanol or propylene glycol; and charcoal treatment. Low boiling alcohol, e.g. methanol may be evaporated off from the filtrate obtained after charcoal treatment. The residue obtained, e.g. containing still alcohol, may be converted into ceftriaxone in the form of a disodium salt, e.g. by suspending ceftriaxone in free form in a mixture of acetone and water and adjusting the pH of the mixture obtained to 4 to 8, preferably to 5.8 in the presence of a sodium source; e.g. the sodium salt of a weak acid, e.g. sodium acetate or sodium bicarbonate. Crystalline ceftriaxone in the form of a disodium salt, e.g. in the form of a heptahydrate, may precipitate and may be isolated. Ceftriaxone in the form of a disodium salt may be obtained in high quality

In the following examples all temperatures are given in degree Celsius.

The following abbreviations are used (herein and in the examples):

- BSA: N,O-bis-(trimethylsilyl)-acetamide
- 5 BSS: bis-(trimethylsilyl)-sulfate
- BSTFA: N,O-bis-(trimethylsilyl)-trifluoroacetamide
- BSU: N,N'-bis(trimethylsilyl)-urea
- Cefotaxime in free form: 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyl-
oxy)methyl-3-cephem-4-carboxylic acid
- 10 Ceftriaxone in free form: 7-[2-(Aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-[[2,5-di-
hydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-
4-carboxylic acid
- Disodium ceftriaxone; 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-[[2,5-di-
hydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-
4-carboxylic acid in the form of a disodium salt
- 15 HMDS: 1,1,1,3,3,3-hexamethyldisilazane
- Sodium cefotaxime: 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyl-
oxy)methyl-3-cephem-4-carboxylic acid in the form of a sodium salt
- TMIS: iodotrimethylsilane
- 20 TMSTf : trimethylsilyl-trifluoromethanesulfonate

Example 1

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid in the form of a disodium salt

Solution A

- 5 18.57 g of 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid, suspended in 185 ml of dichloromethane, are treated under inert gas with 40.69 g of BSA while stirring the mixture at room temperature. The solution obtained is cooled to -10°.

Solution B

- 10 11.2 g of 4-bromo-2(Z)-methoximino-3-oxobutyric acid in 85 ml of dichloromethane, cooled to -10°, are treated under inert gas with 10.41 g of phosphorpentachloride, added in portions, while stirring.

Solution C

- 15 3.81 g of thio urea, suspended in 50 ml of dichloromethane, are treated under inert gas with 40.7 g of BSA while stirring. A clear solution is obtained.

- Solution B is added to solution A while stirring at ca. -10° under an inert gas atmosphere, the mixture obtained is cooled to ca. 0° and treated with solution C under inert gas. The reaction mixture obtained is stirred at ca. 0° and poured while stirring onto an ice-cooled solution of
- 20 41.5 g of sodium 2-ethylhexanoate in 250 ml of acetone/water. The mixture obtained is stirred in an ice bath and 250 ml of water and 500 ml of dichloromethane are added. The pH of the two-phase system obtained is adjusted with sodium bicarbonate solution to 6.5. A two-phase system is obtained. The organic phase is separated off and the pH of the aqueous phase is adjusted to 3 with 2 N HCl. Precipitation occurs. The precipitate obtained is filtrated off and
- 25 suspended in 250 ml of acetone and 15 ml of water. The pH of the suspension obtained is adjusted to 6.5 by addition of 1 M aqueous sodium acetate. A clear solution is obtained and crystallization occurs. Acetone is added while stirring. The precipitate obtained is filtrated off and dried. Ceftriaxone in the form of a disodium salt and in the form of a hemiheptahydrate is
- 30 obtained.

Example 2

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid in the form of a disodium salt

Solutions A and B are produced as described in Example 1, but using in solution B 8.98 g of 4-chloro-2(Z)-methoximino-3-oxo-butyric acid instead of 11.2 g 4-bromo-2(Z)-methoximino-3-oxo-butyric acid. Solutions A and B are mixed and poured onto a suspension of 21.0 g of sodium bicarbonate in 340 ml of water/2-propanol while stirring. The pH of the two-phase system
 5 obtained is adjusted with 2 N HCl to 2.0. The organic phase is separated off and treated with 8.25 ml of water, 4.45 g of triethylamine and 3.35 g of thiourea while stirring. Precipitation occurs. The precipitate is isolated, suspended in 250 ml of acetone and 15 ml of water and treated with 1 M aqueous sodium acetate in water. A clear solution is obtained and
 10 crystallization occurs. Acetone is added under stirring to the mixture obtained. Ceftriaxone in the form of a disodium salt and in the form of a hemiheptahydrate is obtained.

Example 3

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic
 15 acid

Solutions A and B are produced according to a method as described in Example 2, but using in solution A 18.57 g of 7-aminocephalosporanic acid instead of 18.57 g of 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-4H-1,2,4-triazin-3-yl]thio]methyl]-3-cephem-4-carboxylic acid. While stirring the mixture obtained is poured onto an ice-cooled suspension of potassium
 20 bicarbonate in a mixture of water and 2-propanol. The pH of the two-phase system obtained is adjusted to 2.0 with 2 N HCl. The organic phase is separated off and treated with 7.5 ml of water and 3.81 g thiourea while stirring. The pH of the mixture is kept between 3.0 and 3.5 by addition of a solution of 2-amino-2,4,4-trimethylpentane in dichloromethane. A precipitate is obtained. 2-Propanol is added to the suspension obtained while stirring and the precipitate is
 25 isolated and dried. 7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid is obtained.

Example 4

30 Ceftriaxone in free form

Solution A

23.87 g of sodium cefotaxim in 100 ml of dichloromethane are treated under inert gas with 19.31 g of BSTFA while stirring. To the mixture obtained 10.01 g of TMIS are added. The mixture obtained is cooled to 0° and treated with further 20.02 g of TMIS while stirring.

Solution B

- 5 7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 32 ml of dichloromethane are treated with 11.19 g of BSA. A clear solution is obtained.

- Solution B is added to Solution A and the mixture obtained is stirred under inert gas. The mixture obtained is poured onto a mixture of 20.5 g of sodium acetate in 350 ml of water/methanol, the mixture obtained is treated with 6.20 g of sodium thiosulphate pentahydrate and 250 ml of water and 500 ml of dichloromethane are added. The pH of the two-phase system obtained is adjusted to 6.5 with sodium bicarbonate. The organic phase is separated off and the aqueous phase is treated with charcoal. From the mixture obtained the charcoal is filtrated off and the pH of the filtrate obtained is adjusted to 3.0 with 2N HCl.
- 15 Ceftriaxone in free form precipitates and is filtrated off.

Examples 5 and 6

Ceftriaxone in free form

- Are carried out according to the method as described in example 4; but using a Solution A (Example 5) and a Solution A (Example 6) as described below instead of a Solution A as described in Example 4. Ceftriaxone in free form is obtained.
- 20

Solution A (Example 5)

- 23.87 g of sodium cefotaxime in 100 ml of dichloromethane are treated with 8.88 g of HMDS while stirring under inert gas. The mixture obtained is treated at ca. 0° with 11.01 g of TMIS, and with further 20.01 g of TMIS.
- 25

Solution A (Example 6)

- 22.77 g of cefotaxim in free form in 100 ml of dichloromethane are treated with 19.37 g of HMDS while stirring under inert gas. The mixture obtained is treated at ca. 0° with 20.01 g of TMIS and is further stirred.
- 30

Example 7

Disodium ceftriaxone

Ceftriaxone sodium obtained according to example 5 in 2500 ml of methanol is stirred with charcoal. The charcoal is filtrated off and solvent from the filtrate obtained is evaporated off at 30-35°. To the evaporation residue obtained 500 ml of acetone and 100 ml of water are added. The pH of the mixture obtained is adjusted to 5.8 with 5 M aqueous sodium acetate.

- 5 Crystallisation occurs and is completed by addition of acetone. The precipitate obtained is filtrated off, washed with acetone and dried. Crystalline disodium ceftriaxone in the form of a hemiheptahydrate in a purity of 99.4 % (HPLC, area) and a content of 83.7 % is obtained.

Reference Example

10 Disodium ceftriaxone without isolation of ceftriaxone in free form

- Solution A and Solution B, produced according to Example 5, are reacted according to the description in Example 5 and worked up according to the description in Example 5; but omitting adjusting the pH of the aqueous solution obtained after filtrating off the charcoal and omitting isolation of ceftriaxone in free form according to Example 5. Instead, the aqueous
- 15 solution obtained after filtrating off the charcoal according to the description in Example 5, is treated with 350 ml of acetone and the pH of the mixture obtained is adjusted to 5.8 with 5 M aqueous sodium acetate solution according to the description in example 7. The turbid solution obtained is seeded with disodium ceftriaxone obtained according to example 7. Crystallisation starts and is completed by addition of acetone according to the description 7. Crystalline
- 20 dinatrium ceftriaxone is isolated and dried according to the description 7. Crystalline disodium ceftriaxone in the form of a hemiheptahydrate in a purity of 98.1 % (HPLC, area) and a content of 52.6 % is obtained.

Example 8

25 Disodium ceftriaxone

Solution A

23.87 g of sodium cefotaxime in 100 ml of dichlormethane are treated with 30.31 g of BSS while stirring under inert gas in an ice-bath.

Solution B

- 30 7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazine in 32 ml of dichloromethane are treated with 32.18 g of BSTFA while stirring and refluxing for several hours.

Solution B is added to solution A while stirring. The resulting mixture is treated under ice-cooling and inert gas with 38.90 g of TMSTf. The mixture obtained is poured into an ice-cooled solution of 20.5 g of sodium acetate in 350 ml of methanol/water and 250 ml of water and 500 ml of dichloromethane are added. The pH of the two-phase system obtained is adjusted
 5 with aqueous bicarbonate to 6.5. The organic phase is separated off and the aqueous phase is treated with charcoal. The charcoal is filtrated off and the pH of the filtrate obtained is adjusted to 3.0 with 2N HCl. A precipitate forms and the mixture is stirred in an ice-bath. The precipitate is filtrated off. The residue is dissolved in 3000 ml of methanol and treated with charcoal. The charcoal is filtrated off and solvent of the filtrate obtained is evaporated off at
 10 30-35°. The evaporation residue obtained is treated with mit 300 ml of acetone and 150 ml of water adjusting the pH to ca. 5.8 with 5 M aqueous sodium acetate. To the mixture obtained 1500 of ml acetone are added and crystallisation occurs. The crystalline precipitate is filtrated off and dried.

Disodium ceftriaxone is obtained in a purity of 99.9% (HPLC, area).
 15

Example 9

Disodium ceftriaxone – one pot procedure

23.87 g of cefotaxime in free form and 7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 150 ml of dichloromethane are treated with 57.92 g of BSTFA while stirring
 20 under inert gas. A solution obtained is refluxed for several hours, cooled in an ice-bath, and treated with 33.34 g of TMSTf. The mixture obtained is poured onto an ice-cooled solution of 20.5 g of sodium acetate in 350 ml of methanol/water and 250 ml of water and 500 ml of dichloromethane are added. Further treatment and work-up is carried out according to the method described in example 8.

25 Disodium ceftriaxone is obtained in a purity of 99.6% (HPLC, area).

Example 10

Disodium ceftriaxone - one pot procedure

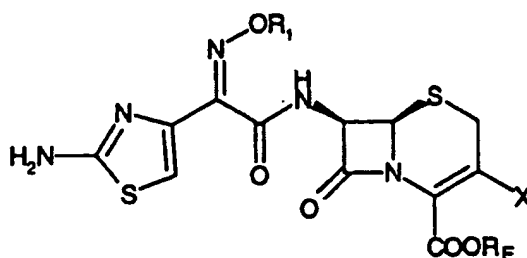
27.12 g of cefotaxime in free form and 8.12 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 100 ml of dichloromethane are refluxed under inert gas with 10.42 g of
 30 BSU. A precipitate obtained is filtrated off and the filtrate obtained is diluted with 100 ml of dichloromethane. 13.86 g of TMSTf are added to the mixture obtained under reflux. Under ice-cooling 5 g of ethanol and 7.5 g of triethylamine are added. A precipitate is obtained and is

filtrated off. The solid residue is dissolved in 100 ml of propylene glycol, treated with charcoal and filtrated. The pH of the filtrate obtained is adjusted to 5.2 with 5 N aqueous sodium acetate. Crystallization occurs while adding acetone.

5 Disodium ceftriaxone is obtained as a fine, crystalline precipitate in a purity of 98.2% (HPLC, area).

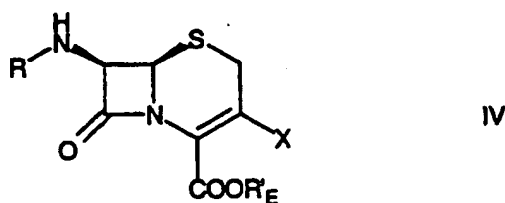
Patent Claims

1. A process for the production of a compound of formula

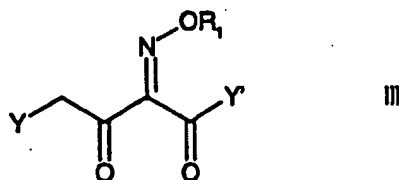


wherein X and R₁ are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO- group to which R_E is attached is an ester, comprising

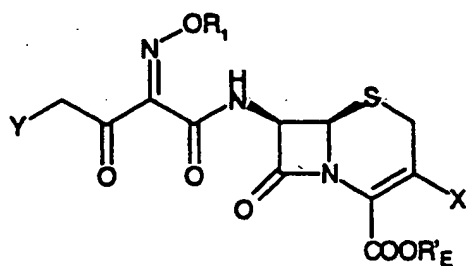
- i) reacting a compound of formula



wherein R is hydrogen or silyl, R'_E is silyl or together with the COO- group to which R'_E is attached is an ester; and X is as defined above, with a compound of formula



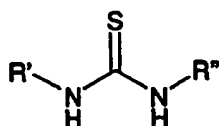
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R₁ is as defined above, to obtain a compound of formula



II

wherein Y, X, R'E and R₁ are as defined above;

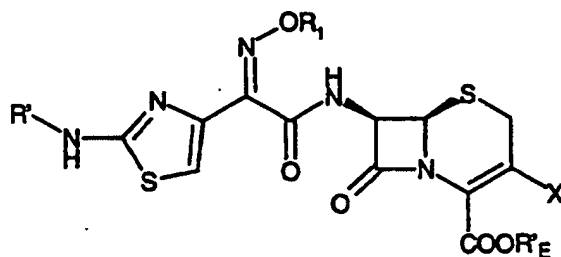
- ii) reacting a compound of formula II wherein X, Y, R'E and R₁ are as defined above, with a compound of formula



V

5

wherein R' is hydrogen or silyl and R'' is silyl; to obtain a compound of formula



VI

10

wherein X, R₁, R' and R'E are as defined above, and desilylating a compound of formula VI to obtain a compound of formula I; or

- li') desilylating a compound of formula II wherein Y, X, R'E and R₁ are as defined above, and reacting a desilylated compound of formula II with thiourea in a solvent system containing organic solvent and water; to obtain a compound of formula I.

15

2. A process for the production of a compound of formula I, wherein X, R₁ and R'E are as defined in claim 1, comprising reacting a compound of formula II, wherein Y, X, R'E and R₁ are as defined in claim 1, with a compound of formula V, wherein R' and R'' are as defined in claim 1 according to step ii) as defined in claim 1; or

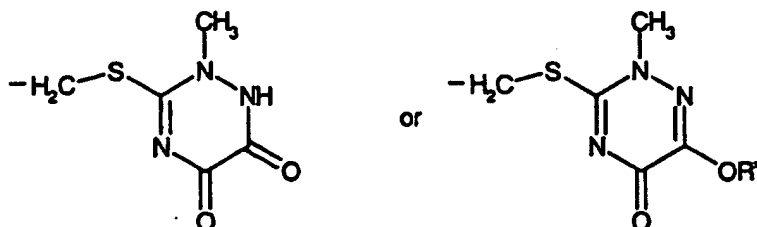
20

- desilylating a compound of formula II, wherein Y, X, R'E and R₁ are as defined in claim 1, and reacting a desilylated compound of formula II with thiourea according to step li') as defined in claim 1, to obtain a compound of formula I.

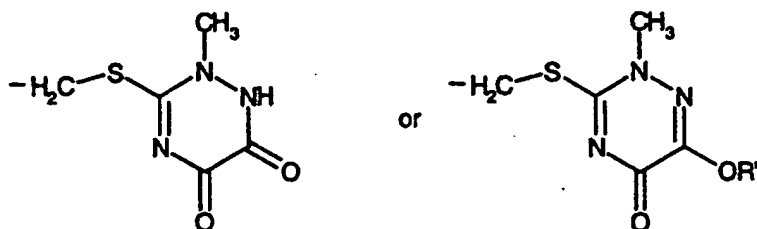
3. A process according to any one of claims 1 to 2 wherein a compound of formula I is ceftriaxone or cefotaxime.

4. A process according to any one of claims 1 to 3 wherein a compound of formula I is in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt, and in the form of a solvate.

5. A process for the production of ceftriaxone in the form of a disodium salt comprising reacting a compound of formula II, wherein Y is as defined in claim 1, R₁ is CH₃, R'_E is silyl, and X is a group of formula



wherein R'' is silyl, with a compound of formula V, wherein R' and R'' are as defined in claim 1, to obtain a compound of formula VI, wherein R'_E is silyl; R₁ is CH₃, R' is as defined in claim 1 and X is a group of formula



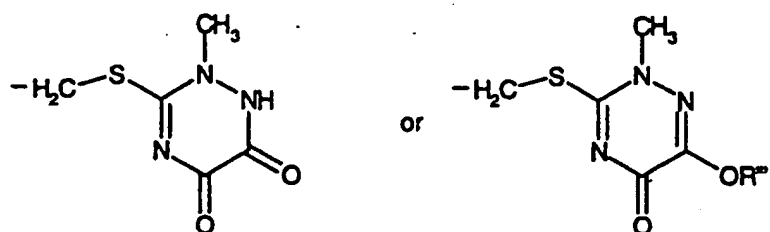
wherein R''' is as defined above; and

- i) reacting the reaction mixture obtained with water/organic solvent which is miscible with water and a base; and with water/organic solvent which is able to form a two-phase system with water;
- ii) adjusting the pH of the mixture obtained to about 6.5;
- iii) separating off the organic solvent from the two-phase system obtained;
- iv) adjusting the pH of the aqueous phase obtained to a pH of about 3;
- v) filtrating off the precipitate formed;

- vi) suspending the precipitate obtained in a mixture of water and organic solvent which is miscible with water;
- vii) adjusting the pH of the mixture obtained to about 6.5; and
- viii) isolating ceftriaxone in the form of a disodium salt.

5

6. A compound of formula II as defined in claim 1, wherein R'_E , R_1 and Y are as defined in claim 1 and X denotes a group of formula



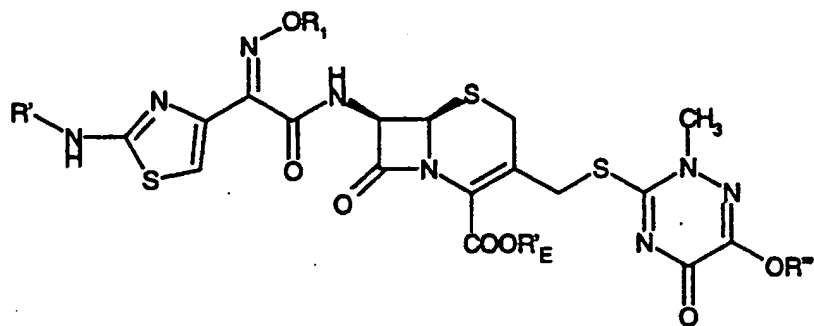
wherein R'' is silyl.

10

7. A compound of formula V as defined in claim 1, wherein R' is hydrogen or $\text{tri}(C_{1-4})\text{alkylsilyl}$, and R'' is $\text{tri}(C_{1-4})\text{alkylsilyl}$.

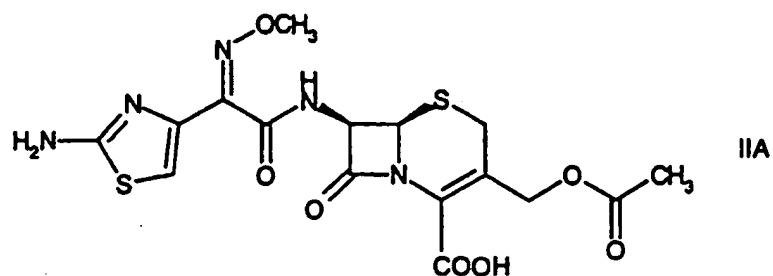
8. A compound of formula

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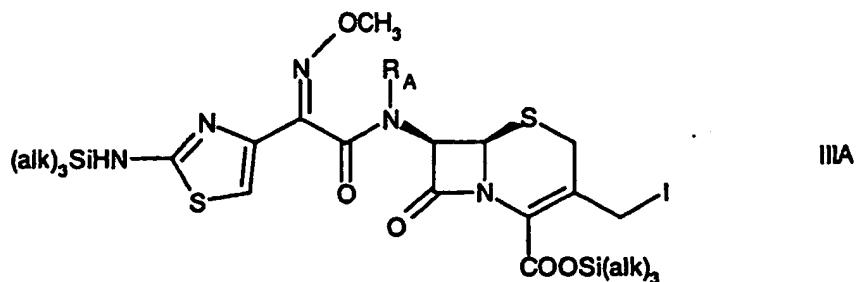


wherein R_1 is as defined in claim 1 and R' , R'_E and R'' are $\text{tri}(C_{1-4})\text{alkylsilyl}$.

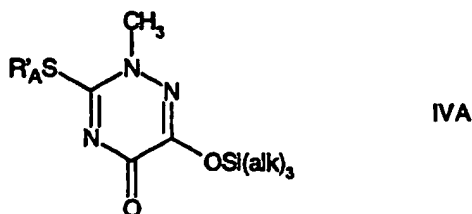
- 20 9. A process for the production of ceftriaxone in the form of a disodium salt comprising
- i) silylating a compound of formula



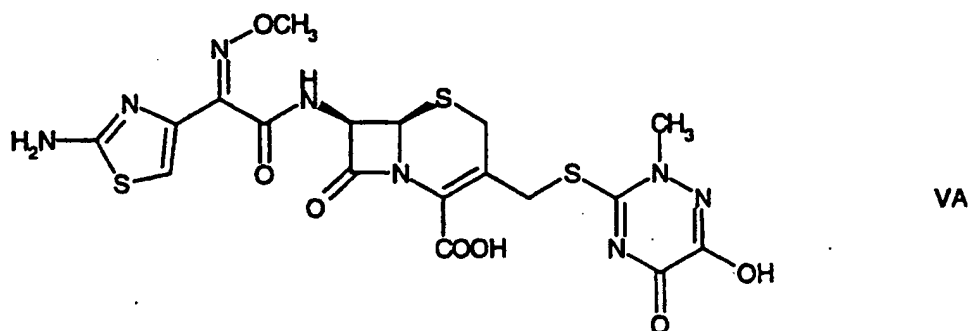
or a compound of formula IIA in the form of a salt and iodinating; to obtain a compound of formula



- 5 wherein R_A is hydrogen or trialkylsilyl and alk is alkyl,
 ii) reacting a compound of formula IIIA obtained in step i) with a compound of formula



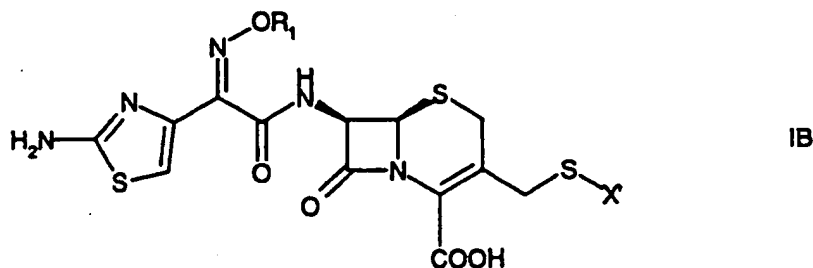
- 10 wherein R'_A is hydrogen or trialkylsilyl, e.g. trimethylsilyl; and desilylating, to obtain a compound of formula



- iii) isolating a compound of formula VA obtained in step ii) from the reaction mixture; and

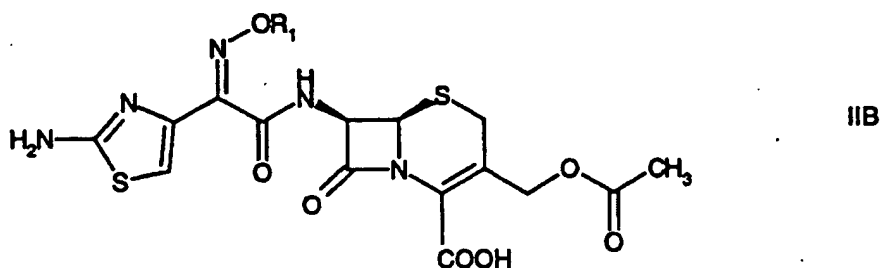
iv) converting a compound of formula VA obtained in step iii) into ceftriaxone in the form of a disodium salt.

10. A process for the production of a compound of formula

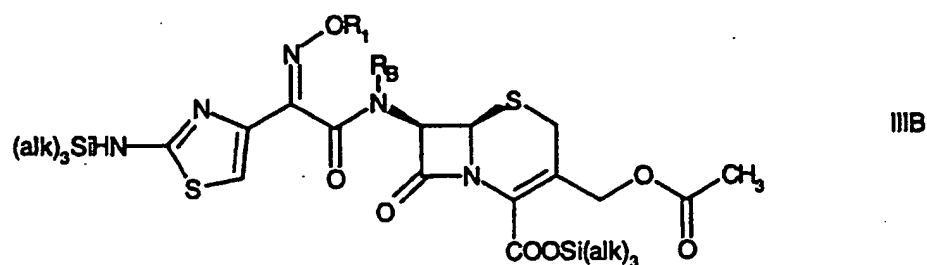


wherein X' and R_1 are substituents useful in cephalosporin chemistry; comprising

i) silylating a compound of formula



or a compound of formula IIB in the form of a salt, wherein R_1 is as defined above, to obtain a compound of formula



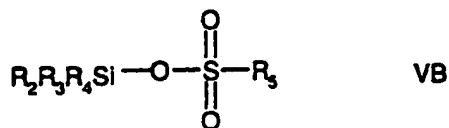
wherein R_8 is hydrogen or trialkylsilyl, and alk is alkyl;

ii) reacting a compound of formula IIIB with a compound of formula



IVB

wherein R'_8 is hydrogen or trialkylsilyl and X' is as defined above, in the presence of a compound of formula



5

wherein R_2 , R_3 and R_4 independently of each other are aryl or alkyl, and R_5 is alkyl or aryl; and

iii) isolating a compound of formula IB from the reaction mixture obtained in step ii).

10

11. A process according to claim 10 wherein in step ii) a compound of formula VB is trimethylsilyl-trifluoromethanesulfonate.

12. A process according to an one of claims 10 to 11, wherein ceftriaxone is produced.

15

13. A process according to anyone of claims 10 to 12, wherein a compound of formula IB is obtained in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt and in the form solvate.

20 14. A process according to any one of claims 10 to 13, wherein ceftriaxone in free form is isolated from the reaction mixture and is converted into ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate.

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/06 C07F7/10 C07F7/18

B. FIELDS SEARCHED

IPC 7 C07D C07F

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP 0 791 596 A (LUPIN LAB LTD) 27 August 1997 (1997-08-27) the whole document	1-14
A	EP 0 556 768 A (BIOCHEMIE GMBH) 25 August 1993 (1993-08-25) the whole document	1-14
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

26/07/2000

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Chouly, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 123, no. 5, 31 July 1995 (1995-07-31) Columbus, Ohio, US; abstract no. 55587, WINIARSKI J. ET AL: "Method of preparing ceftriaxone" XP002142191 abstract & PL 163 399 A (POLSKA AKADEMIA) 31 March 1994 (1994-03-31)</p>	1-14
X	<p>W. WALTER ET AL: "N-(Trimethylsilyl)thioharnstoffe" LIEBIGS ANNALEN DER CHEMIE., no. 2, 1979, pages 263-277, XP002142189 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0170-2041 the whole document</p>	7
X	<p>M. GRUBER ET AL.: "Eine neue Bildungsweise der Phosphor-Phosphor-Bindung." CHEMISCHE BERICHTE - INORGANIC AND ORGANOMETALLIC CHEMISTRY - A EUROPEAN JOURNAL., vol. 123, no. 6, 1990, pages 1313-1317, XP002142190 VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM., DE ISSN: 0009-2940 the whole document</p>	7

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